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**26-AUG-99**

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Subject: Response to Draft Guidance for Industry: Changes to an Approved NDA or ANDA, (Federal Register, 28-June-99, Docket No. 99D-0529)**

To Whom It May Concern:

Novartis Pharmaceuticals Corporation has reviewed the above referenced draft guidance. Specific comments, identified by line number, are provided in tabular form in the enclosure.

It is Novartis' position that the draft Guidance and associated draft revision to CFR 314.70 and CFR601.12 would be improved with additional clarification of certain elements contained therein, as well as delineation of specific data which the Agency will require to support various possible manufacturing and control changes for drugs and biologicals. The numerous cross references to other guidance documents, some of which have not yet been seen in draft form, could contribute to a potentially contradictory situations, and do not provide the benefits of regulatory relief envisioned under FDAMA.

Further, several presentations and discussions occurred at the FDA Public Meeting of August 19, 1999 concerning this proposed draft Guidance and draft rule. Novartis concurs with the PhRMA recommendations that appropriate evaluation and issuance of these key regulatory documents require the Agency to closely consider the issues of conflicting, confusing, or otherwise contradictory regulatory guidances. Novartis therefore recommends that the Agency:

- publish a formal second draft with an additional review and comment period for such revised version of this draft Guidance which incorporates comments from all involved parties received during the first review period.

Thank you for the opportunity to comment. If you have any questions, please contact Dr. Mathias Hukkelhoven at (973)-781-6035 or Leslie Martin-Hischak at (973) 781-3758.

Sincerely,

Dr. Mathias Hukkelhoven
Vice President, Head US DRA
Drug Regulatory Affairs

99D-0529

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

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# Novartis' Comments on the Draft Guidance

# 'Changes to an Approved NDA or ANDA'

# June 1999 (Docket No. 99D-0529)

## General Comments

1. Overall comment – this Guidance captures and ties together several of the SUPAC guidances and maintains enough flexibility to allow for additional guidances to be introduced. In principle, this approach allows for ongoing regulatory improvements without requiring wholesale revision of existing guidances.

   However, to effectively achieve this regulatory intent, absolute clarity and consistency of terminology among the various guidances is necessary. Otherwise, regulatory "drift" may occur. Therefore, it is recommended that this draft Guidance be revised to clarify and use terminology and definitions consistent with other extant/draft guidances and regulatory submission strategies recommended in these guidances. Some examples of inconsistencies are provided in the table below.

2. This Guidance endorses the concept of comparability protocols, thereby potentially easing a subsequent regulatory submission type by focusing on "validating" "effect of the change" work up front, generally based on a pre-approved protocol.

   In the event there is no previously approved protocol (currently approved applications) – does the historical approach used define a protocol? Or does a specific protocol need to be prepared and approved prior to generating the data? If there is no protocol, does the filing type automatically flip into a more restrictive filing type? A Guidance for Comparability Protocols clarifying the requirements is requested.

   For future Applications, is the Agency amenable to comparability protocols as part of new original Applications?

3. This draft guidance focuses on safety and efficacy as determined by bioavailability. This focus needs to be tempered with the fact that bioavailability is not absolutely predicted by dose or in cases where an in vivo - in vitro correlation is weak. Thus, some changes in process or drug substance physical characteristics may have little effect on product performance due to the nature of the active ingredient or formulation technology.

4. A list or relevant regulations and guidances such as is provided in the newly issued Container Closure guidance is recommended for cross reference purposes.

| Lines | Comments |
|---|---|
| Lines 23-40, 105 | The draft guidance provides few recommendations on "change assessment validation", in addition, it refers in general terms to other guidance documents (SUPAC, BACPAC) which have not been written specifically to address change assessment validation. Consequently, there is significant room for misinterpretation of the data requirements to support specific changes.<br>In addition, the use of the term validation may be confused with cGMP requirements such as process validation; therefore, use of the phrase *"assess the change"* or *"change assessment validation"* is recommended. |
| Lines 54-56 | Novartis is sympathetic to the concept that the definition of extraordinary hardship should be reserved for serious or unplanned events. However, to require either a catastrophic event such as a fire or a drug shortage as a means of obtaining expedited FDA Supplement review may put industry in the position of affecting the public health by way of a drug shortage if intended changes to not go as planned. Novartis recommends that lines 55-56 be changed to "reserved for manufacturing changes made necessary by catastrophic events (e.g. fire), by events that could not be reasonably foreseen and for which the applicant could not plan, *or by planned events that have experienced unanticipated delays*" |
| Lines 65-73 | As per 314.70 (c) (5)(ii): If necessary information is not included in a typical NDA supplement (changes been effected), is the FDA determination of compliance with this section requirements (with the addition of more information) equivalent to an approval of the supplement? What is the timeline for FDA action on review of additional requested information after receipt at the Agency? |
| Line 89 | Please clarify proposed listing of changes in the "annual report" cover letter. Please add in an allowance to include the information in an attachment. This will be more confidential (not subject to FOI) and also simplify and shorten the cover letter |
| Lines 97-100 | This information should be moved to the Labeling section of this Guidance. |
| Lines 150-153 | As per earlier comment at lines 65-68 with respect to the recommendation to consult the FDA reviewer, it is likely that inconsistent or inappropriate requests may occur dependent on Division or product dosage form (creeping regulation). |
| Lines 164 | Guidance on how to establish a predetermined "equivalence interval" needs to be provided, in particular for newer products with less commercial production experience. This provision provides that products do not need to be *identical* pre- and post-change for the change to be acceptable, so an appropriate definition of "equivalence interval" is needed. |
| Lines 216-221 | Recommend changing the guidance so that a site may require prior approval (i.e., substantial impact) when the manufacturing process change requires this according to the current SUPAC-IR/MR/SAS guidances. "Materially differ" is vague and non-specific and has broad implications to increase regulatory burden. Clarify if a PAI is required for any changes if the site has been inspected previously for this type of operation. |
| Line 258 (Section VI.B.1) | For a change in synthesis of drug substance, add *"except if used to manufacture or process a drug substance intermediate as per VI.C.2.a and b (lines 303-309) or VI.D.6 (lines 328-332)"*. Purchase of a previously in-house manufactured intermediate should be SNDA CBE-30. |
| Line 252 | If the facility was at one time qualified to perform certain processes, it should continue to be qualified for the process as long as it has a current cGMP inspection and has continued to perform similar approved processes. Clarify what a "current" cGMP inspection means with respect to time since last inspection. |
| Lines 259- | Cross-contamination appears to be a cGMP issue and does not need to be |

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| 260 | addressed in this Guidance. |
| Line 262 | #4 is especially unclear. If everything is changed a prior approval supplement is needed regardless of whether or not the process is moved. |
| Line 265 | Insert "*movement of steps of these manufacturing processes involving process steps or primary packaging not critical to dosing of the product may be handled as per VI.C.I.a (SNDA CBE-30)*". |
| Line 266-267 | Strike "modified release solid oral dosage forms" from Major category and add to Moderate. (CBE-30) The actual site will have minimal impact on the performance of the product characteristics as presented within site-specific stability argument - the real issue is the process validation, not the site. |
| Line 302 | Suggest making this a separate category (D) and changing annual reports to E. This will be more clear and result in 4 types of submissions instead of 3 (one with 2 subgroups). |
| Lines 314-326 (Section VID.1 and 2 | Add "*or contract facility where the new facility has the capability to perform the intended operation*". |
| Line 322 | Footnote No. 9 should be placed at the end of No. 4 as well. |
| Line 333 | Footnote No. 9 should be placed at the end of the section as well. |
| Line 386 | Differences in the scale of lyophilization equipment will most likely change the processing time. These changes should not require a prior approval supplement unless the process is for a sterile product. |
| Line 408, Lines 411-412 | Fundamental is vague and not defined<br>Strike this example. The example presented is only a change of equipment principles within the unit operation of drying, falling within present SUPAC Guidances. The danger of not addressing this is that it could be interpreted that any changes of equipment Class would constitute a "fundamental" change, requiring a Prior Approval Supplement. |
| Lines 421-423 (Section VII.B.6 | Suggest the wording be changed to "*individual components of the ink*" have not been used in CBER/CDER approved products in the past. Please note where a listing of approved inks can be found. |
| Line 466 | Need definition of starting material/cross reference. |
| Lines 617-621 | This appears to be a new requirement, not found in the just issued Container Closure Guidance and should be deleted. |
| Lines 638-639 | Dimensional size changes are often nominal and do not affect product integrity. All changes should not require a prior approval supplement. |
| Line 647 | A change in secondary packaging components is listed as CBE-30 days. These components are generally cartons and are not specified in the NDA. Therefore, they should not be the subjects of a supplement. The phrase "as otherwise listed" is a vague catch-all that has broad regulatory implications and should be deleted or made more specific. |
| Line 711 | Secondary packaging components are not usually filed and need not be the subject of changes in an annual report. |
| Line 778 | We recommend comparability protocols be made SNDA CBE-30, so that the benefit of this regulatory strategy is not lost to Agency review time. |

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